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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,975	11/19/2001	Olga Bandman	PF-0227-2 CIP	9661

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INCYTE CORPORATION
3160 PORTER DRIVE
PALO ALTO, CA 94304

EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,975	BANDMAN ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-38* is/are pending in the application.

4a) Of the above claim(s) *23,26,28,37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24,25,27 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

The Amendment filed February 13, 2004 in response to the Office Action of September 10, 2003 is acknowledged and has been entered.

Claims 22-38 are pending.

Claims 23, 26, 28, 37-38 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 22, 24-25, 27, 29-36 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 22, 24-25, 27, 29-36 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility for the reasons of record in Paper No. 9 and for the reasons set forth below.

As a first, applicants point out that the Examiner erroneously referred to the HUPAP protein as a serine kinase. The Examiner apologizes for the apparent oversight wherein applicant's point out that the specification teaches that HUPAP is a serine protease which

appears to function in the prostate gland. Regardless, the rejection of record is maintained as neither the specification nor any art of record teaches what the HUPAP protein is, how it functions, or a specific and well-established utility for any of the fragments claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease.

Applicants attempt to overcome the rejections of record by pointing out alleged deficiencies in the applied prior art of record. For example, Applicants argue (page 7) that the teachings of Bowie et al. are directed to studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. Applicants further argue that the teachings of Lazar *et al.* and Burgess *et al.* (page 8) are not relevant to the case at hand because in both of these references, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. Applicants argue that these mutations for "artificially" created in the laboratory and are therefore not analogous to molecular evolution. These arguments have been carefully considered but are not found persuasive. Each of the references contributes to the broader teaching that biological function and activity is extremely dependent on the three-dimensional structure and chemical composition of proteins. Therefore, each of the amino acids that contribute to the structure of a protein is of critical importance. Clearly, the teachings of these references must be taken into consideration when the asserted utility of an unknown protein is based, in part, on its structural similarity to other known and well-recognized proteins. For example, in the instant case, HUPAP is asserted to have a 38% amino acid similarity to bovine enterokinase. Thus, based on the general teachings in the art, and those set

forth in Bowie *et al.*, Lazar *et al.*, and Burgess *et al.*, one of ordinary skill in the art would reasonably question the effect of a 62% difference in amino acid composition between the known enterokinase and the purported HUPAP protein. And, and it cannot be predicted, based on the information in the specification, what affect this difference has on the function of the protein. However, Applicants further attempt to rectify this difference by pointing out that there is a threshold value for accepting a certain degree of amino acid differences. Applicants argue (page 8) that Brenner et al. teach that a 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. This argument has been considered but is not found persuasive as Brenner *et al.* go on to point out that a 30% identity was a reliable threshold for plotting the percent identity of unrelated proteins in a *particular* database- the PDB90D-B database (Protein Data Bank comprising domains with were all less than 90% identical) which contains over 2000 protein domains- (page 6074, 2nd column, 2nd paragraph, and Figure 3). In contrast, applicant is comparing the sequence identity of an unknown protein against the sequence of one known protein. Thus, from a statistical view, one of ordinary skill would conclude that applicant does not have the quantity of data to extrapolate the results of Brenner *et al.* Furthermore, Brenner *et al.* teach that high percent identity does not necessarily identify related proteins (Figure 2) wherein the principal reasons percentage identity does so poorly seems to be that is it ignores information about gaps and about the conservative or radical nature of residue substitutions (page 6076, 2nd column, 1st paragraph). Put into context, consider the teachings of Scott *et al.* (Nature Genetics, 1999, 21:440-443). Scott *et al.* teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was

deemed to be a member of sulfate transport proteins because there was 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott *et al.* go on to suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Applicants further disagree and with the Examiner's contention that mRNA expression does not correlate with or predict polypeptide expression. Applicants argue (page 10) that regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification and protein turnover. Applicants further argue that while steady state mRNA levels are "not always directly proportional" to the amount of protein produced in a cell, mRNA levels are routinely (emphasis added) used as an indicator of protein expression. Applicants refer to exhibit A (Lewin, B.) to illustrate that for most genes a major control point probably exists at the level of transcription during the interaction of RNA polymerase with its promoter. In contrast, Applicants argue that the references cited in the previous action represent comparatively unusual mechanisms of gene regulation downstream of transcription. Extrapolating from Lewin, applicants argue that the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 correlates with the levels of SEQ ID

NO:2 mRNA. These arguments have been carefully considered but are not found persuasive. Even if gene regulation occurred predominately at the level of transcription initiation, such an observation does not provide evidence to refute the unpredictability of equating mRNA production with the corresponding polypeptide, because, as applicants noted (page 11), there are many steps in the pathway leading from DNA to protein, and *all* of them can in principle be regulated. Further, the allegation that post-transcriptional regulation, in comparison to regulation at the initiation of transcription, is an unusual event (i.e. rare event) may be attributed to less research in the area of post-transcriptional regulation. Jansen *et al.* (Pediatric Res., Vol. 37, No. 6, 1995 pages 681-686) teach that regulation of mRNA translation, although less well characterized than the regulation of gene transcription, is now recognized as one of the major regulatory steps in the control of gene expression. Thus, while the initiation of gene transcription may represent a highly regulated step, it is also recognized that post-transcriptional events represent major steps in the control of gene expression.

Thus, applicants have not provided a reasonable nexus between 1) the assertion that mRNA levels are usually a good indicator of protein levels with 2) the knowledge that regulation of genes occurs at the level of transcription because there are many steps in the pathway leading from DNA to protein and regulation during the initiation of transcription does not necessitate ruling out gene regulation during later steps. In fact, Lewin acknowledges that control of gene expression can occur at multiple levels, and moreover states that "production of RNA cannot inevitably be equated with production of protein" (Exhibit A, Lewin, 1st page of Chapter 29).

Applicants further disagree (pages 7-8) with the notion that for the claimed antibodies (to be used as a surrogate for a diseased state) the protein must serve as a clinically relevant

diagnostic marker, it must be present in cancer tissue to the exclusion of normal tissue or vice versa. Applicants submit that the Examiner has acknowledged the differential expression of the "polynucleotide" encoding the claimed polypeptide wherein such recognition is sufficient to indicate the presence of cancer and does not require the complete exclusion of the marker in one tissue versus the other. This argument has been considered but is not found persuasive because applicant's arguments are directed solely to the experiments that quantify nucleic acid expression. As set forth above and previously, the disclosure and arguments of record do not provide sufficient evidence to support the assertion that the mRNA levels are predictive of the *claimed* protein's level in a cell. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

Claims 22, 24-25, 27, 29-36 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 22, 24-25, 27, 29-36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record. Applicants argue that the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art. Applicants attest that

the specification provides an adequate written description of the recited variants and fragments of SEQ ID NO:1 and antibodies which bind specifically to them. Applicants further maintain that the specification discloses preferred "variants" and that chemical and structural features of HUPAP are identified. This argument has been considered but is not found persuasive as the alleged variants and or fragments do not define a genus, only one particular species of an isolated polypeptide and a antibody that is specific for said polypeptide. Applicants further attempt to differentiate the claimed subject matter with the decisions in the *Lilly* and *Fiers* cases. This argument has been fully considered but is not deemed persuasive because as a practical matter, the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions. While recitation of structure is indeed an important factor, mere recitation of structure and a product-by-process type of limitation, is insufficient to meet the written description requirement. As set forth previously, the written description in this case only sets forth an isolated antibody which specifically binds to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to antibodies which bind naturally occurring amino acid sequences having at least 90% sequence identity to the sequence of SEQ ID NO: 1 and antibodies which bind to an immunogenic fragment of at least 15 contiguous amino acids of SEQ ID NO:1, all of which read on antibodies that bind allelic variant polypeptides. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.

Applicant's comments regarding the restriction requirement in light of *In re Ochiai* have been noted and will be taken into consideration if any claimed subject matter becomes allowable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

May 06, 2004

GARY NICKOL
PRIMARY EXAMINER